WEST Search History

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DATE: Wednesday, March 08, 2006

Hide?	Set Name	Query	Hit Count
		DB=PGPB,USPT,EPAB; PLUR=YES; OP=OR	
☐	L28	L27 and L14	13
☐	L27	heart or cardia$	181932
☐	L26	L25 not @ay>2000	26
☐	L25	L24 and agonist	117
☐	L24	L23 and hedgehog	178
☐	L23	infarction	29260
☐	L22	L18 and L14	0
☐	L21	L20 not @ay>2000	12
☐	L20	L19 and agonist	89
☐	L19	L18 and hedgehog	257
☐	L18	myocardi$	42582
☐	L17	L6 and myocardial	8
☐	L16	L6 and myocardia	5
☐	L15	L14 and ischemia	13
☐	L14	L13 and L6	17
☐	L13	porter.in.	5981
☐	L12	L11 and L8	53
☐	L11	L10 with L6	53
☐	L10	small adj3 molecule	54166
☐	L9	L8 and L6	134
☐	L8	angiogenesis or proliferation or vascularization	97624
☐	L7	L6 and L4	22
☐	L6	hedgehog with agonist	141
☐	L5	L4 and L1	18
☐	L4	angiogenesis	21878
☐	L3	6683108.pn.	1
☐	L2	L1.ti.	3
☐	L1	hedgehog adj antagonist	80

END OF SEARCH HISTORY

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NEWS 5	DEC 14	2006 MeSH terms loaded for MEDLINE file segment of TOXCENTER
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NEWS 7	DEC 21	IPC search and display fields enhanced in CA/CAplus with the IPC reform
NEWS 8	DEC 23	New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/ USPAT2
NEWS 9	JAN 13	IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
NEWS 10	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to INPADOC
NEWS 11	JAN 17	Pre-1988 INPI data added to MARPAT
NEWS 12	JAN 17	IPC 8 in the WPI family of databases including WPIFV
NEWS 13	JAN 30	Saved answer limit increased
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NEWS 15	FEB 21	STN AnaVist, Version 1.1, lets you share your STN AnaVist visualization results
NEWS 16	FEB 22	Status of current WO (PCT) information on STN
NEWS 17	FEB 22	The IPC thesaurus added to additional patent databases on STN
NEWS 18	FEB 22	Updates in EPFULL; IPC 8 enhancements added

NEWS EXPRESS FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT
http://download.cas.org/express/v8.0-Discover/

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FILE 'HOME' ENTERED AT 15:22:01 ON 27 FEB 2006

=> file medline
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'MEDLINE' ENTERED AT 15:22:09 ON 27 FEB 2006

 FILE LAST UPDATED: 23 FEB 2006 (20060223/UP).  FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 is now (26 Feb.) available.  For details
 on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s hedgehog
          3649 HEDGEHOG
           852 HEDGEHOGS
L1        4017 HEDGEHOG
                (HEDGEHOG OR HEDGEHOGS)

=> s myocardial
        244527 MYOCARDIAL
             3 MYOCARDIALS
L2      244527 MYOCARDIAL
                (MYOCARDIAL OR MYOCARDIALS)

=> s l2 and l1
L3          12 L2 AND L1

=> s l3 not py>2000
       2934825 PY>2000
                (PY>20009999)
L4           9 L3 NOT PY>2000

=> d ibib 1-9

L4   ANSWER 1 OF 9     MEDLINE on STN
ACCESSION NUMBER:   2000465512     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 11021439
TITLE:              Cardiomyopathy in captive African hedgehogs
                    (Atelerix albiventris).
AUTHOR:             Raymond J T; Garner M M
CORPORATE SOURCE:   Northwest ZooPath, Snohomish, WA 98296-4815, USA.
SOURCE:             Journal of veterinary diagnostic investigation : official
                    publication of the American Association of Veterinary
                    Laboratory Diagnosticians, Inc, (2000 Sep) Vol. 12, No. 5,
                    pp. 468-72.
```

Journal code: 9011490. ISSN: 1040-6387.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010125

L4 ANSWER 2 OF 9 MEDLINE on STN
ACCESSION NUMBER: 96426701 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8828980
TITLE: How often has Lp(a) evolved?.
AUTHOR: Lawn R M
CORPORATE SOURCE: Falk Cardiovascular Research Center, Stanford University School of Medicine, CA 94305-5246, USA.
SOURCE: Clinical genetics, (1996 Apr) Vol. 49, No. 4, pp. 167-74.
Ref: 61
Journal code: 0253664. ISSN: 0009-9163.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961210

L4 ANSWER 3 OF 9 MEDLINE on STN
ACCESSION NUMBER: 94273536 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8004994
TITLE: Microcalorimetric study on **myocardial** metabolism in a hibernator and two nonhibernators at 20 degrees C and 37 degrees C.
AUTHOR: Ikomi-Kumm J; Monti M; Hanson A; Johansson B W
CORPORATE SOURCE: Department of Internal Medicine, Lund University Hospital, Malmo, Sweden.
SOURCE: Cryobiology, (1994 Apr) Vol. 31, No. 2, pp. 133-43.
Journal code: 0006252. ISSN: 0011-2240.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 199407
ENTRY DATE: Entered STN: 19940729
Last Updated on STN: 19940729
Entered Medline: 19940715

L4 ANSWER 4 OF 9 MEDLINE on STN
ACCESSION NUMBER: 91138357 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2286096
TITLE: Mechanical restitution at different temperatures in papillary muscles from rabbit, rat, and **hedgehog**.
AUTHOR: Liu B; Wohlfart B; Johansson B W
CORPORATE SOURCE: Department of Pharmacology, University of Lund, Sweden.
SOURCE: Cryobiology, (1990 Dec) Vol. 27, No. 6, pp. 596-604.
Journal code: 0006252. ISSN: 0011-2240.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199103
ENTRY DATE: Entered STN: 19910412
Last Updated on STN: 19910412
Entered Medline: 19910326

L4 ANSWER 5 OF 9 MEDLINE on STN
ACCESSION NUMBER: 91065005 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2249456
TITLE: Effects of low temperature on contraction in papillary muscles from rabbit, rat, and **hedgehog**.
AUTHOR: Liu B; Wohlfart B; Johansson B W
CORPORATE SOURCE: Department of Pharmacology, University of Lund, Sweden.
SOURCE: Cryobiology, (1990 Oct) Vol. 27, No. 5, pp. 539-46.
Journal code: 0006252. ISSN: 0011-2240.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199101
ENTRY DATE: Entered STN: 19910308
Last Updated on STN: 19910308
Entered Medline: 19910115

L4 ANSWER 6 OF 9 MEDLINE on STN
ACCESSION NUMBER: 87029426 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3769518
TITLE: Effects of induced hypothermia on organ blood flow in a hibernator and a nonhibernator.
AUTHOR: Sjoquist P O; Duker G; Johansson B W
SOURCE: Cryobiology, (1986 Oct) Vol. 23, No. 5, pp. 440-6.
Journal code: 0006252. ISSN: 0011-2240.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198611
ENTRY DATE: Entered STN: 19900302
Last Updated on STN: 19900302
Entered Medline: 19861125

L4 ANSWER 7 OF 9 MEDLINE on STN
ACCESSION NUMBER: 86108432 MEDLINE
DOCUMENT NUMBER: PubMed ID: 4085517
TITLE: Ventricular repolarization and fibrillation threshold in hibernating species.
AUTHOR: Johansson B W
SOURCE: European heart journal, (1985 Nov) Vol. 6 Suppl D, pp. 53-62.
Journal code: 8006263. ISSN: 0195-668X.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198603
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860311

L4 ANSWER 8 OF 9 MEDLINE on STN
ACCESSION NUMBER: 85100400 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6518802

TITLE: Cardiac responses in relation to heart size.
AUTHOR: Johansson B W
SOURCE: Cryobiology, (1984 Dec) Vol. 21, No. 6, pp. 627-36.
Journal code: 0006252. ISSN: 0011-2240.
Report No.: NASA-85100400.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 198502
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19850226

L4 ANSWER 9 OF 9 MEDLINE on STN
ACCESSION NUMBER: 62045823 MEDLINE
DOCUMENT NUMBER: PubMed ID: 13904450
TITLE: **Myocardial** lactate concentration in guinea-pigs, normothermic and hypothermic, and **hedgehogs**, in a hibernating and a non-hibernating state.
AUTHOR: HANSON A; JOHANSSON B W
SOURCE: Acta physiologica Scandinavica, (1961 Oct) Vol. 53, pp. 137-41.
Journal code: 0370362. ISSN: 0001-6772.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: OLDMEDLINE; NONMEDLINE
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 19990716
Last Updated on STN: 19990716
Entered Medline: 19981101

=> file pctfull

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	2.31	2.52

FILE 'PCTFULL' ENTERED AT 15:23:24 ON 27 FEB 2006
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FILE LAST UPDATED: 21 FEB 2006 <20060221/UPTX>
MOST RECENT UPDATE WEEK: 200607
FILE COVERS 1978 TO DATE

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FORMAT CHANGES <<<

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ONLY, USE FIELD CODE FPI <<<

>>> SDI SEARCHES (ALERTS) WILL BE RESUMED WHEN BIBLIOGRAPHIC DATA
BECOME AVAILABLE <<<

=> s hedgehog
1002 HEDGEHOG
55 HEDGEHOGS

```
L5        1029 HEDGEHOG
                 (HEDGEHOG OR HEDGEHOGS)

=> s myocardial
L6       17861 MYOCARDIAL

=> s l6 and l5
L7         165 L6 AND L5

=> s structure or formula or compound
         418360 STRUCTURE
         206597 STRUCTURES
         455983 STRUCTURE
                  (STRUCTURE OR STRUCTURES)
         151185 FORMULA
          24694 FORMULAS
          25119 FORMULAE
         158696 FORMULA
                  (FORMULA OR FORMULAS OR FORMULAE)
         204205 COMPOUND
         215366 COMPOUNDS
         263248 COMPOUND
                  (COMPOUND OR COMPOUNDS)
L8       578073 STRUCTURE OR FORMULA OR COMPOUND

=> s l8 and l7
L9         163 L8 AND L7

=> s l9 not py>1999
         630082 PY>1999
L10         18 L9 NOT PY>1999

=> s agonist
          25066 AGONIST
          27468 AGONISTS
L11       34707 AGONIST
                  (AGONIST OR AGONISTS)

=> s l11 and l10
L12           6 L11 AND L10

=> d ibib 1-6

L12    ANSWER 1 OF 6     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:       2006009836 PCTFULL
       no bibliographic data available - please use FPI for PI information
DESIGNATED STATES

L12    ANSWER 2 OF 6     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:       2006008342 PCTFULL
       no bibliographic data available - please use FPI for PI information
DESIGNATED STATES

L12    ANSWER 3 OF 6     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:       2006006948 PCTFULL
       no bibliographic data available - please use FPI for PI information
DESIGNATED STATES

L12    ANSWER 4 OF 6     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:       1999064627 PCTFULL  ED 20020515
TITLE (ENGLISH):        PROBES USED FOR GENETIC FILING
TITLE (FRENCH):         SONDES UTILISEES POUR PROFILAGE GENETIQUE
INVENTOR(S):            ROBERTS, Gareth, Wyn
```

PATENT ASSIGNEE(S): GENOSTIC PHARMA LIMITED;
ROBERTS, Gareth, Wyn
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9964627	A2	19991216

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.:	WO 1999-GB1780	A	19990604
PRIORITY INFO.:	GB 1998-9812099.1		19980606
	GB 1998-9813291.3		19980620
	GB 1998-9813611.2		19980624
	GB 1998-9813835.7		19980627
	GB 1998-9814110.4		19980701
	GB 1998-9814580.8		19980707
	GB 1998-9815438.8		19980716
	GB 1998-9815576.5		19980718
	GB 1998-9815574.0		19980718
	GB 1998-9816085.6		19980724
	GB 1998-9816086.4		19980724
	GB 1998-9816921.2		19980805
	GB 1998-9817097.0		19980807
	GB 1998-9817200.0		19980808
	GB 1998-9817632.4		19980814
	GB 1998-9817943.5		19980819

L12 ANSWER 5 OF 6 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1999056785 PCTFULL ED 20020515
TITLE (ENGLISH): MUSCLE-DERIVED CELL MEDIATED GENE DELIVERY FOR TREATING MUSCLE- AND BONE-RELATED INJURY OR DYSFUNCTION
TITLE (FRENCH): TRANSPORT DE GENE EFFECTUE PAR L'INTERMEDIAIRE D'UNE CELLULE DE MUSCLE PERMETTANT DE TRAITER LES LESIONS OU LES DYSFONCTIONS MUSCULAIRES OU OSSEUSES
INVENTOR(S): CHANCELLOR, Michael, B.;
HUARD, Johnny
PATENT ASSIGNEE(S): UNIVERSITY OF PITTSBURGH
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9956785	A2	19991111

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.:	WO 1999-US9451	A	19990430
PRIORITY INFO.:	US 1998-60/083,917		19980501

L12 ANSWER 6 OF 6 PCTFULL COPYRIGHT 2006 Univentio on STN

ACCESSION NUMBER: 1998035020 PCTFULL ED 20020514
TITLE (ENGLISH): METHODS FOR MODULATING HEMATOPOIESIS AND VASCULAR GROWTH
TITLE (FRENCH): PROCEDES DESTINES A MODULER L'HEMATOPOIESE ET LA CROISSANCE VASCULAIRE
INVENTOR(S): BARON, Margaret, H.;
FARRINGTON, Sarah, M.;
BELAOUSSOFF, Maria
PATENT ASSIGNEE(S): THE PRESIDENTS AND FELLOWS OF HARVARD COLLEGE
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9835020	A2	19980813

DESIGNATED STATES
W: CA JP AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
APPLICATION INFO.: WO 1998-US2633 A 19980210
PRIORITY INFO.: US 1997-60/037,513 19970210
US 1997-60/049,763 19970616

=> d kwic 6

L12 ANSWER 6 OF 6 PCTFULL COPYRIGHT 2006 Univentio on STN
ABEN Methods and assays are provided for selecting **compounds** that are functionally equivalent to a gene product expressed in an embryo's extraembryonic tissue for use in modulating hematopoiesis and vascular growth, such **compound** being exemplified by a **hedgehog** protein, and an **agonist** of a **hedgehog** protein binding receptor. According to the method, such **compound** causes undifferentiated mesodermally derived cells to undergo at least one of hematopoiesis or vasculogenesis. Examples of undifferentiated mesodermally derived cells. . .
ABFR . . . d'un embryon. Ces procedes sont destines a moduler l'hematopoiese et la croissance vasculaire, le compose etant notamment une proteine a **structure** dite en herisson, ainsi qu'un agoniste d'un recepteur de liaison de proteine a **structure** dite en herisson. Conformement a ce procede, un tel compose permet de soumettre a hématopoiese ou developpement du systeme vasculaire. .
.

DETD . . . mesodermally derived cells, to undergo at least one of hematopoiesis and vascular growth. The method includes the steps of selecting a **compound** that is functionally equivalent to a gene product expressed in an embryo's extraernbryonic tissue; and causing the **compound** to access the cells, so as to stimulate the cells to undergo at least one of hernatopoiesis and vascular growth.
. . .
in vascular growth or hernatopoiesis in an embryo in utero, that includes the steps of: selecting an effective dose of a **compound** that is functionally equivalent to a gene product expressed in an extraembryonic tissue; and causing the **compound** to access a population of embryonic cells in vivo, so as to stimulate the cells to

undergo at least one of
hematopoiesis. . .
. . .
treating a subject
suffering from an abnormal number of erythroid cells, that includes the steps of selecting an
effective dose of a **compound** that is functionally equivalent
to a gene product expressed in an
extraembryonic tissue; and causing the **compound** to access a
population of hernatopoietic
stem cells over an effective time so as to modulate the number of cells
undergoing. . .
. . .
for treating a subject
suffering from an ischemia in tissues containing inesoderinally derived cells, that includes
selecting an effective dose of a **compound** that is functionally
equivalent to a gene product
expressed in an extraembryonic tissue; and administering the
compound to the ischemic site
over an effective time so as to stimulate vascular growth.

In another embodiment of the invention, an in vitro assay is provided for determining
the activity of a **compound** capable of modulating
hernatopoiesis or vascular growth, that
includes the steps of selecting a population of cells from a tissue derived. . .

In another embodiment of the invention, an assay is provided for determining the
activity of a **compound** capable of modulating hematopoiesis or
vascular growth, that
includes the steps of selecting a first transgenic animal carrying a marker:E-globin hybrid
1. . . an embryo
from the mating at a time within the first third of the gestation period; and determining the
effect of the **compound** on the stimulation of hematopoiesis and
vascular growth in the
isolated embryo by measuring marker expression.

Fig. 3 shows the formation of yolk sac-like **structures** by
cultured blastocysts (a)
transgenic blastocysts prior to culture (b) Sac-like **structure**
(non transgenic) stained with
benzidine to reveal hemoglobin containing cells (c) Sac from cultured transgenic blastocysts
stained with XGal to reveal hemoglobin. . .

Fig. 4 shows RT-PCR analysis of blastocyst cultures: (A) e-globin was observed in
blastocysts that have developed into sac-like **structures** (sac)
but not in samples that were
relatively flat mounds of cells (flat). The higher molecular weight band is the internal
control-actin.. . .
. . .
but is absent in epiblasts only, as determined by XGal
staining. Dashed lines were drawn around the epiblasts to facilitate visualization of
structures. (a) whole embryo on a filter; (b) epiblast on a
filter; (c) whole embryo on a slide;

and (d) epiblast on. . .

Fig. 9 shows that recombinant **hedgehog** protein can substitute for visceral endoderm to stimulate primitive hernatopoiesis in cultured epiblasts. Isolated epiblasts were cultured in the absence (lanes labeled none) or presence of three different concentrations of recombinant **hedgehog** protein (0.25, 1 and 5 Vg/ml). Primitive hernatopoiesis was assessed by RT-PCR analysis for e-globin expression. Actin served as an internal. . .

The circular **structure** represents a blastocyst of around 3.5 days.

. . .

stem cells and progenitor cells from embryo or adult. Embodiments of the invention are further directed to novel assays for identifying **compounds** capable of stimulating hernatopoiesis and vascular growth. Support for the methods of the invention are provided in the examples contained herein. According to an embodiment of the invention,

compounds have been identified that are capable of stimulating blood development in the embryo and in the adult and are functionally equivalent to gene products expressed in the visceral endoderm and yolk sac mesoderm. Such gene products are exemplified by **hedgehog** **compounds**, TGF-P, TNF, and WNT **compounds** and are here identified as achieving a similar effect to that observed with extraembryonic tissues with regard to hematopoiesis and vascular growth in undifferentiated mesodermal derived tissues. In an embodiment of the invention, **compounds** including those selected from **hedgehog** and TGF-P may act synergistically so as to enhance their stimulatory effect on target cells.

Synergistic effect is defined here as for two or more **compounds** where little or no biological effect is observed with the **compounds** alone but together the **compounds** have a potent biological effect.

Hedgehog **compound** is defined here and in the claims as a class of molecules of the **hedgehog** family that includes recombinant **hedgehog** protein, analogs, and derivatives of **hedgehog** proteins, and **agonists** and antagonists of **hedgehog** protein receptors and functional equivalents of the aforementioned.

. . .

and in the adult. According to embodiments of the invention, processes of vascular growth and hematopoiesis in embryonic development are affected by **compounds** in the visceral endoderm. For example, we have identified for the first time that **hedgehog** proteins act on undifferentiated mesodermal derived cells in vitro to stimulate blood formation and on

embryonic tissue and yolk sac development at very early stages in the hernatopoiesis and
vascular growth pathways. Furthermore, according to the invention, these early acting
compounds have utility in regulating hematopoiesis and
vascular growth in the adult animal.

. . .
addition of visceral endoderm which is sufficient to cause the anterior epiblast to
form blood islands. When either visceral endoderm or **hedgehog** protein was added to the
culture, blood formation was observed. (Figure 16)
(iv) Explants or embryoid bodies derived from mutants defective in. .
.
. . .
visceral endoderm such that its absence results in the failure to make blood, is a
suitable model system for screening novel **compounds** from
libraries such as those derived
from extraembryonic tissues, where these libraries include combinatorial peptide libraries and
recombinant DNA libraries. By using a pooling strategy to reduce the number of
experimental tests, **compounds** may be identified that are
useful in modulating hematopoiesis
and vascular growth in embryoid bodies.
. . .
type of assay can be used to study the effect of other mutations, such as
deficiency of signaling factors such as **hedgehog** proteins (for example, Indian **hedgehog**), on
blood formation.(Examples 3-5) For example, Ihh null mutant ES cells may be formed and
factors capable of overcoming the mutation, identified.. These cells could be rescued either
by providing exogenous **hedgehog** protein or by transfecting the cells with vectors expressing
a **hedgehog** gene utilizing standard vectors or retroviral
vectors.(Figure 9) The mutated cells
could also be reintroduced into mice to form chimeras.
. . .
assay for expression of many
genes from a single culture product.(Figure 4)
Using the above assays, we have identified a number of **compounds** that are
functionally equivalent to gene products that are expressed in extraembryonic tissues and
may stimulate blood fori-nation. These **compounds** include TGF-P proteins more specifically
TGF-P I more specifically bone morphogenic protein (BMP) more specifically BMP-4; tumor
necrosis factor (TNF) proteins more specifically TNF-a; wnt family; and **hedgehog** proteins.

(Figures 5,9 and 17) **Compounds** may also include naturally
occurring and synthetic **agonists,**
antagonists, analogs and derivatives of the above. These molecules may interact with
membrane proteins which initiate signal transduction pathways resulting in a biological
response. Therefore, in addition to the above **compounds,**
agonists and antagonists to these
membrane binding proteins including those receptors, receptor

agonists and receptor
antagonists associated with **hedgehog** binding receptors and
hedgehog signalling transduction
pathways such as smoothened, patched and gli may have utility in
regulating hernatopoiesis
and vascular growth.

G) screening libraries of **compounds** for activity in
stimulating hernatopoiesis and
vascular growth;
(ii) testing for the effect of growth factors, cytokines and other
signaling
molecules on embryonic hernatopoiesis and also on vascular growth;
(iii) determining the effect of **hedgehog** proteins on
hematopoiesis and vascular
growth in the embryo, fetus and adult. For example, the blastocyst assay
may be used to
determine the effect of **hedgehog** proteins on yolk sac'
development ex vivo where the
blastocyst is derived from transgenic or non-transgenic animals.
. . .
mesoderm is of the same
origin as that of the yolk sac;
(v) following the development of primitive erythroid cells and vascular
structures
by staining with a marker such as XGal so as to outline the vasculature
and permit the
tracking of vascular growth as. . . individual explants of targeted
mutations in genes
that affect hematopoiesis or vascular growth in the parent animal
including those carrying
transgenes expressing **hedgehog**, patched, Gli and other
proteins; and
(vii) examining the effect of gene therapy on mesodermally derived
tissues; where
for example, the gene for **hedgehog** protein is introduced into
prestreak embryos deprived of
the visceral endoderm, under various promoters so as to modulate the
effect of. . .

Hedgehog proteins: We have shown here for the first time that
hedgehog proteins are
capable of stimulating hernatopoiesis in the yolk sac, and the
splanchnopleura and other
hematopoietic tissues of the embryo or fetus. . . of the
adult.(Examples 3-5, Tables 1-2, Figs 6,9). By screening for molecules
that
were present in the visceral endoderm, we identified **hedgehog**
gene product. When a
hedgehog protein (SHH) was added to epiblast cultures and RNA
was isolated after 2-3 days
and analyzed by RT-PCR (Example 3, Fig.. . .

The above assays show that **hedgehog** proteins expressed in
extraembryonic tissue as
well as **hedgehog** proteins that are closely related to proteins
expressed in extraernbryonic
tissues, stimulate hernatopoiesis and vasculogenesis. Members of the
hedgehog family which
are a distinct family of signaling molecules (e.g., reviewed in Goodrich
et al.,Genes &
Develop. 10 (1996), 301-12) are known. . . spermatogenesis. The
family was initially identified as

involved in normal segmental patterning in Drosophila (Nusslein-Volhard et al, Nature, 287
(1980), 795-801). The **hedgehog** family includes Desert **hedgehog** (DHH) protein, Indian
hedgehog protein (IHH), Moonrat **hedgehog** (Zebrafish) and Tiggy winkle **hedgehog** (Zebra
fish).

The utility of the **hedgehog** proteins in stimulating hematopoiesis and vascular growth
is further reinforced by our experiments on target molecules through which these proteins act.

In support of our observations that **hedgehog** proteins are capable of stimulating
hematopoiesis, we identified the enriched expression of Gli and patched in yolk sac
mesoderm. Gli is a transcription factor involved in the transduction pathway on which
hedgehog proteins act, while PTC (patched) is a membrane protein that binds **hedgehog**
protein to initiate the signal transduction pathway that ultimately causes a biological response
in the target cell. The association of these proteins with yolk sac mesoderm further supports
the observation that **hedgehog** proteins stimulate hematopoiesis. Since ptc is the presumed
gateway to a cell response, any **agonist** of **hedgehog** capable of binding patch is expected to
induce the same biological effect as **hedgehog**-in this case, hematopoiesis and vascular
growth.

Certain **hedgehog** proteins have been reported to be involved in the initiation of
expression of the secondary signaling molecules-BMP-2 and BMP-4 (proteins belonging. . . to
the TGF-P family) in the mesoderm and Fgf-4 in the ectoderm (WO 95/18856). We have
identified for the first time, that **hedgehog** proteins might interact in a synergistic manner with
secondary signaling molecules to stimulate hematopoiesis and vascular growth (Example 6).

The activity of **compounds** that are functional equivalents to a gene product expressed
in extra-embryonic tissue such as recombinant **hedgehog** protein, analogs, derivatives and
dissociation products of **hedgehog** proteins, and **agonists** of **hedgehog** protein receptors such
as PTC according to the invention, may stimulate hematopoiesis and vascular growth by
1 5 acting on cells or. . .

The invention includes the use of functional peptides of **hedgehog** protein. The term
functional peptide as a subclass of a **hedgehog** **compound** defined above, is meant to
include peptide fragments of the **hedgehog** protein that are capable of inducing a biological
activity that is the same or equivalent to the entire protein (WO 96/16668, incorporated here
by reference). The invention further includes **hedgehog**

compounds described in WO
95/18856 and here incorporated by reference, including homologs of **hedgehog** proteins,
recombinant **hedgehog** proteins, **hedgehog** encoding
nucleic acids, antisense molecules, gene
constructs for use in gene therapy including viral vectors known in the art, combinatorial
mutants of **hedgehog** proteins as **agonists** or
antagonists, and antibodies specific for **hedgehog**
protein epitope. These and other **compounds** may be selected for modulating hernatopoiesis
and vascular growth according to the assays of the invention.

. . .

invention, these factors may be used to stimulate hematopoiesis and vascular growth in animals including mammals, including humans. Similarly antagonists to
the **compounds** of the invention may be used to inhibit vascular
growth and hematopoiesis.

Our novel blastocyst assay may be used to determine the effect of **hedgehog** proteins
on yolk sac development. In addition, blastosacs could be assayed for gene expression not
only using LacZ as a histochemical marker,. . .

Transgenic mouse models for studying the effect of selected **compounds** on hematopoiesis
and vascular growth.

. . .

al. J.Biol. Chem. Vol 270, (1995) pp 1289-1294). Other transgenic mice may be formed in
which a selected sequence from the **hedgehog** gene family may be placed under control of an
enhancer and/or promoter of the sort described above. Furthermore, transgenic mice may be
generated in which the **hedgehog** or **hedgehog**
agonist or antagonist is expressed under the
control of heterologous tissue specific promoters/enhancers such as described above. Other
transgenic animals may be formed in which **hedgehog** regulatory sequences are used to drive
expression of heterologous gene coding sequences in specific embryonic or adult tissues eg
Ihh regulatory sequences. . .

Science vol 269 (1995)pp 679-682, to target **hedgehog** genes
into selected sites in the
genome under the control of endogenous sequences in embryonic stem (ES) cells. These
modified ES cells. . .

. . .

to blood diseases such as leukemias, and abnormal vascular growth and abnormal
hernatopoiesis. These events may be analyzed with regard to **hedgehog compounds**.

There are a number of therapeutic applications for **compounds** of the invention. Such
uses are associated with the modulation of hematopoiesis and vascular growth and include
methods that result in stimulation as well as those that result in inhibition of proliferation
and/or differentiation of stem cells. Examples of **compounds** of

the invention have been
discussed above.

(a) therapeutic **compounds** such as **hedgehog** proteins
including derivatives,
analogs, and degradation products of naturally occurring proteins;
agonists or antagonists of
protein receptors as well as functional equivalents of the above listed
compounds. The
therapeutic **compounds** may be isolated from cultures of
extra-embryonic tissues,
manufactured by recombinant technology or prepared by synthetic
chemistry;
(b) coding sequences for the above- listed therapeutic **compounds**
, incorporated
into vectors suited for gene therapy techniques; and
(C) mammalian cells that have been transformed with coding sequences of
the
above for. . .

. . .
of the techniques available
in the art. For example, a protein, analogue, derivative, antagonist or
receptor, of an
identified protein (collectively called **compounds**) such as
hedghog related **compounds**, may
be introduced into a vector and the vector introduced into the
appropriate target tissue where
this tissue is located in an. . . enhancer to ensure selective
expression in the targeted tissue. For
example, use of the cardiac actin enhancer to express the desired
compound in the heart, the
MCK enhancer to express the **compound** in skeletal muscle; sca-I
regulatory sequences to
1 5 express **hedgehog compound** in hematopoietic stem
cells or a retina-specific regulatory
element of the interphotoreceptor retinoid-binding protein to express
the **compound** in the
retina.

. . .
heterologous cells contained within an immune protective barrier, may be
manipulated by standard techniques to secrete the selected protein such
as **hedgehog**, or
analogues, derivatives, antagonists or receptors of protein.

. . .
lineages. Examples of targets for such treatments include in vivo or in
vitro exposure of undifferentiated mesodermally derived cells to a
compound of the
invention. Examples of target cells include bone marrow stem cells,
progenitor cells, and
cord blood cells. These cells may be. . . or the cells may be freshly
isolated and maintained in vitro in a culture
medium., Exposure of such cells to the **compound** results in
enhanced proliferation and/or
differentiation of the cells, the stimulated cells being implanted in
the same or different
subject from which. . .

. . .
from disease caused by
infectious agents such as human immune deficiency virus and may be
treated using a method
1 0 and **compounds** that stimulate hematopoiesis. The
consequences of such abnormalities if
untreated are various forms of anemia (associated with abnormally low

levels of
erythrocytes).. . .
. . .
degenerative disease, aging, trauma, or infectious agents. Examples include
diabetic chronic ulcers, bums, frost bite, ischernic events following stroke and
transplantation. The **compounds** of the invention may be used in the adult for induction of
revascularization or formation of collateral vessels in ischemic myocardium or ischemic
limbs, and in coronary artery bypasses and in promoting wound healing in general. For
example, **compounds** of the invention may be used in treatment of duodenal ulcers by
enhancing microvessel density and promoting more rapid healing. In. .
.
. . .
5'-ACACGATGCCATGCTGGTCA-3'
c-myosin(5') 5'-CTCGCAGAACAGCAGCCTAA-3' PCR product is 679bp; 32 cycles
c-myosin(3') 5-AGGGTCTGCTGGAGAGGTTA-3'
(C) BLASTOCYSTS ISOLATED AT ABOUT 3 3.5DPC PROVIDE A MODEL SYSTEM FOR SCREENING **COMPOUNDS** THAT CAN STIMULATE HEMATOPOIESIS AND VASCULAR GROWTH OF UNDIFFERENTIATED MESODERMAL CELLS
Blastocyst cultures were prepared and used to analyze the effects of **compounds** on
the stimulation of undifferentiated mesodermal derived cells to undergo hernatopoiesis and
vasculogenesis. The blastocyst culture system described here is suited for following the
development of embryonic **structures** in vitro, such as the yolk sac, that normally form post
implantation in vivo. The effects of exogenously added growth factors.
. .
. . .
(2,000 U/ml),
streptomycin (2,000 pg/ml), 2 niM glutamine, I mM pyruvate, 0. I mM nonessential amino
acids (GIBCO-BRL), and 10-4M P-mercaptoethanol. Sac-like **structures** could first be seen
around 7 days in culture; by 9- 1 0 days they had enlarged to the point where they were easily
visible with the naked eye (0 2 mm in diameter). These sac-like **structures** (here termed
blastosacs) closely resembled early inurine yolk sacs.

4A, embryonic globin is produced only when yolk sac-like **structures** form, but not if the
blastocysts do not progress in their development beyond an amorphous mound of
trophectoderm cells.

Null mutant emblyoid bodies Embryoid bodies are **structures** derived from ES cells
that form blood islands under appropriate culture conditions (Keller (1995)). We have
developed an assay system using embryoid. . . 195) Gene Targeting: A Practical Approach (New York: IRL Press). with mutations in selected genes were rescued
by addition of a **compound** that is functionally equivalent to the gene product expressed by
the non- mutated gene.

Example 3: **Compounds** that are functionally equivalent to a gene product
expressed in an embryo's extraembryonic tissue (exemplified by **hedgehog** protein) stimulate hematopoiesis and vascular growth of
undifferentiated mesodermal cells (exemplified by epiblast mesoderm)
(a) A **hedgehog** protein, typified by Sonic **hedgehog,** was demonstrated to
stimulate hernatopoiesis in the epiblast mesoderm using the method of Example 2(A) (Fig. 9).

(b) **Compounds** that are functionally equivalent to a gene product expressed in an
embryo's extraernbryonic tissue (exemplified by **hedgehog** protein) stimulate hematopoiesis
and vascular growth of undifferentiated mesodermal cells (exemplified by adult bone marrow
cells).

To determine whether recombinant **hedgehog** proteins influence the development or
differentiation of adult hematopoietic stem or progenitor cells, we carried out in vitro clonal
assays. Mononuclear cells. . .
. . .
bovine serum albumin (cell culture grade BSA, 1%), 2-mercaptoethanol (I x I OM) and the indicated growth factors and recombinant **hedgehog**
proteins. Recombinant human erythropoietin (Epo) was obtained from Amgen and used at 40
U/nil. Recombinant interleukin-3 (IL-3) and granulocyte/macrophage-colony stimulating
factor (GM-CSF) were. . . were scored on the days indicted. Colonies were scored as CFU-E, BFU-E, myeloid
or mixed. Where included in the cultures, recombinant **hedgehog** proteins were added at
concentrations between I and 5 yg/ml. Buffer alone (5 mM sodium phosphate pH 5.5
150mM NaCl, 0.5 mM. . .
. . .
all types (erythroid: CFU-E,
BFU-E; myeloid: CFU-GM) were increased by - 1. 5 to more than 4-fold, in a dose-dependent
manner (recombinant **hedgehog** protein added at 1, 2.5, 5yg/ml,
X ug). The observation that
hedgehog proteins are apparently not selective for erythroid versus myeloid lineage is
consistent with the hypothesis that they stimulate stem or early. . .

All three recombinant **hedgehog** proteins stimulated colony formation. From these data we
conclude that both SHH and IHH enhance proliferation, differentiation and/or survival of
hematopoietic stem/progenitor. . .
. . .
were stored in buffer pH 8.0; untagged SHH was stored in buffer pH 5
Other approaches to measuring the effect of **compounds** that are functionally
equivalent to a gene product expressed in an embEyo's extraembryonic tissue on

undifferentiated mesodermal cells.

. . .
by flow cytometry (florescence-activated cell sorting, FACS) or magnetic immunoselection (Testa and Molineux, 1993) and their development
enhanced in the presence of **hedgehog** protein. These resulting populations are examined
using in vivo assays include the CFU`-S assay (spleen colony-forming unit) and long-term
bone marrow cultures. . .

. . .
sac mesoderm. (Fig. 6) The enriched expression
of Gli and patched in yolk sac mesoderm points to mesoderm as target of **hedgehog**
signalling.: Yolk sacs from 10.5 and 12.5 dpc embryos were separated into endoderm (e) and
mesoderrn (m) fractions and RNA was prepared. . .

Example 6: Synergistic effect of **Hedgehog** protein with TGF-P proteins on
1 5 hematopoiesis (and vascular growth)
Using the methods of Example 3(A) above, we have shown using RT-PCR, that both
Indian **Hedgehog** and BMP-6 are expressed in early visceral endoderm. Whole embryo
(6.5dpc), epiblasts, epiblasts plus **hedgehog** protein, epiblasts plus BMP-6 protein and
epiblasts plus **hedgehog** protein and BMP-6; are examined after 72 hrs incubation to
determine the extent of activation Of E-globin expression. The experiment is repeated for
BMP-2, BMP-4 and BMP We expect to observe an enhanced effect when both **hedgehog**
and BMP-4 are present compared with either alone.

CLMEN. . . stimulating a population of undifferentiated mesodermally derived cells to undergo at least one of hematopoiesis and vascular growth; comprising:
(a) selecting a **compound** that is functionally equivalent to a gene product
expressed in an embryo's extraembryonic tissue;
(b) causing the **compound** to access the cells, so as to stimulate the cells to
undergo at least one hernatopoiesis and vascular growth.

2 A method according to claim 1, wherein the **compound** is a secreted protein.

3 A method according to claim 1, wherein the **compound** is a **hedgehog**
compound.

4 A method according to claim 3, wherein the **compound** is an **agonist** of a
hedgehog protein binding receptor.

5 A method according to claim 4, wherein the **hedgehog** protein binding receptor
is patched.

6 A method according to claim 1, wherein the **compound** causes enriched
expression of Gli.

7 A method according to claim 3, wherein the **hedgehog compound** is selected from the group consisting of Indian **hedgehog**, Desert **hedgehog** and Sonic **hedgehog compound**.

8 A method according to claim 3, wherein the **compound** is an Indian **hedgehog compound**,

9 A method according to claim 1, wherein the **compound** is a first **compound** derived from a first gene product and is capable of acting synergistically with a second **compound** that is derived from a second gene product expressed in the extraembryonic tissue, so as to enhance the stimulation of at. . .

10 A method according to claim 9, wherein the second **compound** is a functional equivalent of a TGF-P family member.

. . . further comprising the step of maintaining the cell population in vitro in a culture medium such that step (b) includes providing the **compound** in the culture medium.

. . . to claim 14, wherein the cells are precursor cells from an adult human capable of vascular growth when stimulated by the **compound**.

25 A method according to claim 24, further comprising causing the **compound** to access the stem cells, by administering an effective dose of the **compound** to the animal by any of oral, intradermal, subcutaneous, transmucosal, intramuscular or intravenous routes.

26 A method according to claim 2, wherein the **compound** is functionally equivalent to a protein from the bone marrow morphogenic protein (BMP) family.

. . . of treating developmental errors in vascular growth or hematopoiesis in an embryo in utero, comprising:
(a) selecting an effective dose of a **compound** that is functionally equivalent to a gene product expressed in an extraembryonic tissue; and
(b) causing the **compound** to access a population of embryonic cells in vivo, so as to stimulate the cells to undergo at least one of. . .

28 A method according to claim 27, wherein the **compound** is an **agonist** of a **hedgehog** protein-receptor.

29 A method according to claim 27, wherein the **compound** is a **hedgehog** protein.

30 A method according to claim 27, wherein the **compound** is a first **compound** capable of acting synergistically with a second **compound** that is derived from a second gene

product expressed in the extraernbryonic tissue, so as to enhance the stimulation of
hernatopoiesis in. . .

. . .
A method of treating a subject suffering from an abnormal number of erythroid
cells, comprising:
(a) selecting an effective dose of a **compound** that is functionally
equivalent to a gene product expressed in an extraembryonic tissue; and
(b) causing the **compound** to access a population of hematopoietic stem
cells over an effective time so as to modulate the number of cells undergoing. . .

32 A method according to claim 3 1, wherein the **compound** is an **agonist** of a
hedgehog protein-receptor and the hernatopoietic stem cells are stimulated to undergo one of
proliferation or hematopoiesis.

33 A method according to claim 32, wherein the **compound** is a **hedgehog** protein.

34 A method according to claim 3 1, wherein the **compound** is a first **compound**
capable of acting synergistically with a second **compound** that is derived from a second gene
product expressed in the extraernbryonic tissue, so as to enhance the stimulation of
hematopoiesis in. . .

35 A method according to claim 3 1, wherein the **compound** is an antagonist of a
hedgehog protein and the hematopoietic stem cells are inhibited from undergoing one of
proliferation or hematopoiesis.

38 A method of treating a subject suffering from an ischernia in tissues,
comprising:
(a) selecting an effective dose of a **compound** that is functionally
equivalent to a gene product expressed in an extraeffibryonic tissue; and
(b) administering the **compound** to the ischernic site over an effective time
so as to stimulate vascular growth within the ischernic tissues.

39 A method according to claim 37, wherein the ischerriia is **myocardial** ischernia.

40 A method according to claim 38, wherein the **compound** is an **agonist** of a
hedgehog protein-receptor.

41 A method according to claim 40, wherein the **compound** is a **hedgehog** protein.

42 A method according to claim 39, wherein the **compound** is a first **compound**
that is capable of acting synergistically with a second **compound** that is derived from a second

gene product expressed in the extraembryonic tissue, so as to enhance the stimulation of
vascular growth.

43 A method of treating abnormally enhanced vascular growth in a subject,
comprising:
(a) selecting an effective dose of a **hedgehog compound** capable of
inhibiting the activity of a gene product expressed in an extraembryonic tissue; and
(b) administering the **compound** to the subject over an effective time so as
to inhibit abnormally enhanced vascular growth.

44 An in vitro assay for determining the activity of a **compound** capable of
modulating hematopoiesis or vascular growth, comprising:
(a) selecting a population of cells from a tissue derived from a fertilized
egg of. . .

52 An assay for determining the activity of a **compound** capable of modulating
1 5 hernatopoiesis or vascular growth, comprising:
(a) selecting a first transgenic animal carrying a marker:c-globin hybrid
gene; wherein the. . . animal that is similarly transgenic;
(c) isolating an embryo from the mating during the gestation period; and
(d) determining the effect of the **compound** on the stimulation of
hernatopoiesis and vascular growth in the isolated embryo by measuring
marker expression.